REMARKS/ARGUMENTS

Sua sponte amendment

Claim 54 has been amended. More specifically, the preamble has been amended to recite "aggregates" as well as plaques to describe Applicant's invention with greater particularity.

Objection to the Specification

The disclosure has been objected to because the first paragraph does not contain a reference to the parent applications as required. In response to this objection, Applicant has enclosed a copy of the Application Data Sheet (ADS), which was submitted when the instant Application was originally filed. This ADS contains the relevant priority information. 37 CFR 1.76(b)(5) states that providing this information in the Application Data Sheet constitutes the specific reference required by 35 USC 119(e) or 120.

Rejections under 35 USC 101

Claims 64-78 have been rejected under 35 USC 101 for lack of utility. More specifically, the Patent Office characterizes the relevant teaching as follows:

> The specification teaches that a catalytic antibody that will hydrolyze and/or disaggregate preformed beta-amyloid plaques has been made. In addition, this antibody will cross the blood brain barrier because it will bind to a transferrin receptor. This catalytic antibody was made using a transition state analog containing a statine analog.

Applicant respectfully submits that claims 64-78 are not directed to catalytic antibodies. More specifically, in the Exemplification section of the application as filed (pages 23-60), two sections are presented. Section 1 (pages 23-36) is entitled "Retention of ß-Amyloid in the

Circulation". Section 2 (pages 36-60) is entitled "Eliciting Monoclonal Antibodies With Transition State Antigens". The Patent Office is correct in the characterization of Applicant's teaching in the above-quoted language; however, this teaching is not relevant to the rejected claims. The above-quoted language is referring to experiments described in Section 2 of the Exemplification section whereas experiments relevant to claims 64-78 are described in Section 1 of the application as filed. The Patent Office further states in support of the rejection that:

> Nowhere is the utility of a 'vaccine composition comprising a β-amyloid epitope' taught and/or its utility shown. A 'vaccine composition' infers that the composition confers some immunological protection upon the recipient. Therefore it is maintained that such a composition has no specific substantial utility, absent a very convincing showing to the contrary.

Applicant respectfully traverses this rejection. In Section 1 of the Exemplification section (see page 30, line 10 to page 31, line 8) Applicant teaches vaccine trials in Cynomolgus monkeys with a human-compatible β-amyloid vaccine. Applicant states, "this animal system is highly relevant to human applications since the predicted amino acid sequence of β-amyloid in these primates is identical to humans, and their basic physiology and immunological systems closely approximate those which will be encountered in a clinical situation (page 30, lines 17-21)." Also, Applicant states, "the Cynomolgus monkeys mounted a strong immune response to a single injection of the simplest vaccine preparation composed of the full length human β-amyloid peptide adsorbed to an aluminum hydroxide gel (page 30, lines 25-28)." Applicant further discloses that injection of this vaccine results in the production of antibodies that bind to the full-length β-amyloid peptide and react with its amino-terminal, central and carboxyl-terminal regions (page 30, lines 28-33 and Table 6, page 30).

The binding of a large 150kDa antibody molecule to the much smaller 4kDa amyloid peptide would unavoidably greatly alter the chemical activity, biodistribution and biological actions of β–amyloid in the body. While anti-Aβ antibodies in the circulation cannot cross the

blood-brain barrier to a significant extent, Applicant clearly showed that animals treated with an anti-Aβ antibody retained 10-times more labeled $A\beta_{1-40}$ in the circulation, thereby providing evidence that an Aβ antibody can sequester significant levels of Aβ and alter the equilibrium distribution of Aβ in the body (page 31, line 19 to page 32, line 2 and Table 7). One of skill in the art would readily predict with probable certainty that administration of the same vaccine formulation to a human would result in an immune response similar to that of the Cynomolgus monkeys of Applicant's disclosure, since the Cynomolgus monkeys' "basic physiology and immunological systems closely approximate those which will be encountered in a clinical situation (page 30, lines 19-21)." Administration of the same vaccine formulation to a human would likely be safe since the monkeys were "perfectly healthy, " with "no apparent side effects due to cross-reaction of the anti-Aβ antibodies with naturally occurring β-amyloid precursor protein or other vital components...or autoimmune disease, immune complex disease or any other adverse/toxic reaction to the vaccination (page 30, line 36 to page 31, line 8)." One of skill in the art would readily predict, based on the animal studies described, that immunization of a human with such a vaccine would result in similar sequestration of significant levels of β-amyloid in the circulation.

Because it is well established that the aggregation of β-amyloid and the deposition of β-amyloid as plaques in the brain are both accelerated by an elevation in the extracellular concentration of β-amyloid (Scheuner et al., *Nature Med.* **2**: 864 (1996); Kowall et al., *Proc. Natl. Acad. Sci.* **88**: 7247 (1991)), one of ordinary skill in the art would readily predict that sequestration of significant levels of β-amyloid would lower the extracellular concentration of amyloid and thereby prevent the formation of amyloid plaques within the human brain. Because elevated levels of full-length Aβ in the blood are associated with Alzheimer's disease (Scheuner et al., *Nature Med.* **2**: 864 (1996)), a composition whose administration would result in the

sequestration of amyloid in the blood is clearly useful in preventing and/or treating the disease. Any β-amyloid which is retained or drawn into the circulatory system by its interaction with antibodies would be unavailable for aggregate or plaque formation or other harmful effects in the brain. One of skill in the art would also recognize that administration of a vaccine composition comprising a β-amyloid epitope would result in the formation of immune complexes of β-amyloid with anti-β-amyloid antibodies. The resulting antibody-dependent processes, which are innate to the immune system and well known to one of skill in the art, would clear and/or destroy the β-amyloid antigen from a vaccinated individual. In light of an overwhelming body of genetic, biochemical, and clinical evidence, it is generally accepted that β-amyloid, its aggregates and/or the plaques it forms are the underlying cause of Alzheimer's disease. Therefore, few in the art would argue that neutralizing or removing β-amyloid from the body would not have a beneficial effect in terms of preventing or curing Alzheimer's disease.

Applicant's disclosure, coupled with the state of the art at the time the instant application was filed, further indicates a clear utility for a vaccine composition comprising a β-amyloid epitope. A publication printed prior to Applicant's filing date also confirms that Applicant's invention does, in fact, have utility. International Application No. PCT/US98/25386 demonstrates the prophylactic efficacy of the administration of a β-amyloid peptide in treating Alzheimer's disease (page 32, line 36 to page 33, line 12). Immunizations with a β-amyloid peptide were shown to be effective in reducing the amyloid burden in mice and preventing further amyloid deposition over time relative to a control (page 41, line 13 to page 42, line 8). One of skill in the art would readily believe, based on the teachings of Applicant's disclosure and the knowledge of one of skill in the art at the time of Applicant's filing, that administration of a vaccine preparation comprising a β-amyloid epitope would be effective in stimulating an immune response in a human, the immune response being characterized by the generation of circulating

antibodies which bind specifically to the epitope present on endogenous β-amyloid in the human, thereby inhibiting the formation of both β-amyloid aggregates and plaques in the brain of the human.

Rejections under 35 USC 112

Claims 64-78 have been rejected under 35 USC 112, first paragraph for lack of enablement. More specifically, the Patent Office states:

> ...since the claimed invention is not supported by either a specific substantial asserted utility or a well established utility..., one skilled in the art would not know how to use the claimed invention.

Applicant respectfully traverses this rejection. For the reasons stated above, Applicant asserts that the disclosure of the instant Application coupled with the state of the art at the time the instant application was filed indicates a clear utility for a vaccine composition comprising a β-amyloid epitope. Also for the reasons stated above, Applicant submits that the description of the invention fully satisfies the requirement of 35 USC 112, first paragraph. The Patent Office further states in support of this rejection that:

> Nowhere in the specification is it taught that a catalytic antibody can be made using other than a statine analog and nowhere is it taught that a 'vaccine composition comprising a β–amyloid epitope' that does not meet the other requirements outlined *supra* will cleave β–amyloid or have any other activity...

It is respectfully submitted that none of claims 64-78 of the instant application are drawn to catalytic antibodies. Applicant teaches the use of catalytic antibodies in Section II (Eliciting monoclonal antibodies with transition state antigens) on pages 36-60 in the Exemplification section of the disclosure. Applicant teaches subject matter relevant to the claimed invention in Section I (Retention of β–amyloid in the circulation) on pages 23-36 in the Exemplification section of the disclosure.

Claims 37-59 and 83 have been rejected under 35 USC 112, first paragraph for lack of enablement. More specifically, the Patent Office states:

> The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant specification teaches that an antibody was made using a statine analog of a transition state that would disaggregate preformed β-amyloid plaques...Nowhere is it taught that such an antibody has the ability to inhibit the formation of β-amyloid plaques...

In response, Applicant has cancelled claim 83. With respect to claims 37-59, Applicant respectfully traverses this rejection. It is respectfully submitted that none of claims 37-59 are directed to catalytic antibodies. Applicant teaches the use of catalytic antibodies in Section II (Eliciting monoclonal antibodies with transition state antigens) on pages 36-60 in the Exemplification section of the disclosure. Applicant teaches subject matter relevant to claims 37-59 in Section I (Retention of β–amyloid in the circulation) on pages 23-36 in the Exemplification section of the disclosure. Applicant's disclosure coupled with the state of the art at the time the instant application was filed indicates that administration of a β-amyloid epitope would be effective in inhibiting the formation of β-amyloid aggregates and plaques. Applicant teaches administration of a full-length human β-amyloid peptide to Cynomolgus monkeys in a human-compatible formulation (page 30, lines 12-14). Administration of this peptide resulted in the production of antibodies that bind to the full-length β-amyloid peptide and react with its amino-terminal, central, and carboxyl-terminal regions (page 30, lines 28-33). While anti-Aβ antibodies in the circulation cannot cross the blood-brain barrier to a significant extent, Applicant clearly showed that animals treated with an anti-Aβ antibody retained 10-times more labeled $A\beta_{1-40}$ in the circulation, thereby providing evidence that an Aβ antibody can sequester significant levels of Aβ and alter the equilibrium distribution of Aβ in the body (page 31, line 19 to page 32, line 2).

One of skill in the art would readily predict, based on the animal studies of the instant invention, that immunization of a human with such a vaccine would result in similar sequestration of significant levels of β-amyloid in the circulation. Because it is well established that deposition of β-amyloid as aggregates and plaques in the brain are accelerated by an elevation in its extracellular concentration (Scheuner et al., *Nature Med.* **2**: 864 (1996)), one of ordinary skill in the art would readily predict that sequestration of significant levels of β-amyloid would lower the extracellular concentration of amyloid and thereby prevent the formation of amyloid aggregates and plaques within the brain.

A publication printed prior to Applicant's filing date further confirms that Applicant's invention is, in fact, enabling for teaching an antibody which has the ability to inhibit the formation of β–amyloid plaques. International Application No. PCT/US98/25386 demonstrates the prophylactic efficacy of the administration of a β-amyloid peptide in treating Alzheimer's disease (page 32, line 36 to page 33, line 12). Immunizations with a β-amyloid peptide were shown to be effective in reducing the amyloid burden in mice and preventing further amyloid deposition over time relative to a control (page 41, line 13 to page 42, line 8). One of skill in the art would readily believe, based on the teachings of Applicant's disclosure and the knowledge of one of skill in the art at the time of Applicant's filing, that administration of a β-amyloid epitope would be effective in stimulating an immune response in a human, the immune response being characterized by the generation of circulating antibodies which bind specifically to the epitope present on endogenous β-amyloid in the human, the Aβ antibodies sequestering β–amyloid in the circulation, and the sequestration inhibiting the formation of β-amyloid aggregates and plaques in the brain of the human. One of skill in the art at the time the instant application was filed would readily believe, based on Applicant's disclosure, that administration of a β-amyloid epitope would be effective in inhibiting the formation of β-amyloid aggregates and plaques.

Rejection under 35 USC 102

Claims 64 and 76-78 have been rejected under 35 USC 102(b). More specifically, the Patent Office states that:

> Suzuki et al. teaches in column 15, lines 42-53 a composition of β-amyloid antigens together with Freund's adjuvant. Since the elements of the instant claims are present the description of the composition as a vaccine is immaterial to the patentability of the composition.

In response to this rejection, Claim 64 has been amended to recite a "human compatible" limitation. Support for the "human compatible" limitation is found on page 30, line 15 of the Specification as filed. The cited Suzuki et al. reference is directed toward the production of monoclonal antibodies in non-human animals. This process involves immunization of a non-human animal, followed by the isolation of the spleen or lymph nodes from the animal. Antibody producing cells contained in these tissues are thereafter fused with myeloma cells to generate monoclonal antibody-producing hybridomas. Human compatible adjuvants are not used for routine immunization of non-human animals. Suzuki et al. does not disclose a composition suitable for immunization of humans. Instead, the cited Suzuki et al. reference refers to the use of the composition for immunization of monkeys, rabbits, dogs, guinea pigs, mice, rats, sheep, goat and chickens. The cited reference refers specifically to the use of Freund's complete or Freund's incomplete adjuvant, which is certainly not considered to be a human compatible adjuvant. As stated in Vogel, F. R. (1995) Immunologic Adjuvants for Modern Vaccine Formulations, Annals New York Academy of Sciences; vol. 754, p153-160:

> To date, alum adjuvants...are the only adjuvants approved for use in vaccines licensed by the Food and Drug Administration. Complete Freund's adjuvant... is too reactive to be used clinically.

Applicant therefore submits that the composition of the Suzuki et al reference differs from the composition of the subject patent application. Suzuki et al. does not teach administration of a β-amyloid epitope in a human-compatible vaccine composition and, therefore, it is submitted that the amendment of Claim 64 to recite "human compatible" obviates this rejection.

Rejection Under 35 USC 103

Claims 64-78 have been rejected under 35 USC 103(a) as being unpatentable over either of Suzuki et al. or Anderson. More specifically, the Patent Office states that:

> Since (Suzuki et al.) recites 'β-amyloid antigens,' it is maintained that this reads on all epitopes from all regions of the protein ...Anderson in column 11, lines 26-46 teaches the use of a 'β-amyloid peptide preparation' along with Freund's adjuvant. It is maintained that a 'β-amyloid peptide preparation' reads on all epitopes from all regions of the protein. It is also maintained that claims 77-78 are taught by the reference(s), at least inherently.

With respect to Suzuki et al., the cited reference teaches away from the use of a human-compatible adjuvant. As discussed above, the relevant teaching of the cited reference only relates to the production of monoclonal antibodies. The production of monoclonal antibodies requires the sacrifice of the immunized animal. Clearly the reference teaches away from the use of a human-compatible adjuvant in a composition with a β-amyloid epitope. As for Anderson et al., it also teaches away from the claimed invention. The reference relates, in pertinent part, to the production of monoclonal or polyclonal antibodies in non-human animals. As in Suzuki et al., Anderson teaches a composition of β -amyloid peptide preparation with Freund's adjuvant, a human incompatible adjuvant as discussed above. As was the case with the Suzuki et al. reference, there is no disclosure of, or motivation to use, a human-compatible adjuvant. The cited reference does not contemplate human administration of a β-amyloid

epitope in a human compatible formulation. In fact, the reference specifically states in column 11, lines 12-15, that:

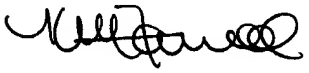
> Once a particular peptide has been found to have an immunological determinant, the peptide can be used to elicit antibody production in naive animals (i.e., animals that have not been previously exposed to human beta-amyloid peptide). (emphasis added)

Clearly a human does not qualify as a naive animal. Furthermore, one of skill in the art would not have been able to predict, based on the teachings of Anderson, that administration of a human β-amyloid epitope to a human, a non-naive animal, would have resulted in the production of an immune response to β-amyloid. Prior to Applicant's discovery, no one had proposed to use a β–amyloid epitope as a basis for a therapeutic vaccine in people because the conventional wisdom taught that a self antigen would not elicit an immune response, and furthermore that if an immune response were elicited against a self antigen, autoimmune disease syndrome would ensue. Thus, like the Suzuki et al. reference, Anderson clearly teaches away from the invention described in Applicant's claims as amended.

Summary

In light of the above amendment, consideration of the subject patent application is respectfully requested. Any deficiency or overpayment should be charged or credited to Deposit Account No. 500282.

Respectfully submitted,



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